Chapter 6

Is Zinc Deficiency Related to Thyroid Dysfunction? 🔓

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Abstract

Thyroid hormones an important role in the development and maintenance of nearly all tissues. Thyroid disorders affect almost all endocrine glands, such as the pituitary gland. Thyroid disorders are increasingly common endocrine abnormalities in all groups in the community. Normal thyroid status depends on the presence of many trace elements to continue the synthesis and metabolism of thyroid hormones. Some trace elements such as zinc (Zn) and copper (Cu) have important roles in regulating biological processes, maintaining normal thyroid function and preventing thyroid diseases. Zn, tetraiodothyronine (T4) acts as the cofactor of the enzyme involved in the conversion of triiodothyronine (T3). Moreover, Zn plays a role in the conversion of pre-prothyrotropin-releasing hormone (TRH). Thyroglobulin (Tg) and thyroid peroxidase (TPO) are two important thyroid-specific proteins and regulate the information transfer process from tissue-specific DNA to RNA in thyroid hormone. In this information transfer process, transcription binding factors containing zinc bound to cysteine are involved. Besides, the increase of thyroid binding proteins increases serum thyroxine levels and Zn is also affected by this increase. In the studies conducted that different results have been determined regarding the effect of zinc on TSH, T3 and T4. The aim of this review is to evaluate whether zinc deficiency has an effect on thyroid dysfunction in accordance with current literature.

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1. INTRODUCTION

Triiodothyronine (T_3) and thyroxine (T_4) are produced and secreted by the follicular cells of the thyroid, an endocrine gland. The homeostasis of the organism is maintained in large part by these hormones. They regulate lipid and glucose metabolism and allow metabolic adaptations to change in energy intake. Besides, these hormones regulate basal metabolism, thermogenesis, and oxidative metabolism (Duntas and Biondi, 2013; Carmona et al. 2014). Thyroid dysfunction affects all tissues in the body because these hormone receptors are located at several tissues that depend on appropriate cell function activities. Furthermore, adequate levels of these hormones are required inside the cell for the target tissues to function normally (Fernández-Real. et al. 2013; Biondi 2010). T_4 is the primary hormone produced by the thyroid gland. Yet, because thyroid hormones have a strong affinity for nuclear receptors, T_3 is biologically more active. Therefore, cell transformation is required by deiodinases from T_4 to T_3 to ensure the functional effectiveness of thyroid hormones (Marsili et al. 2011; Mahan et al. 2012).

Several trace elements are needed to maintain the synthesis and metabolism of thyroid hormones (Alvarez et al. 2015). The trace elements such as zinc (Zn) and copper (Cu) have important roles in regulating biological processes, maintaining normal thyroid function, and preventing thyroid diseases (Maret 2017). Zn acts as the cofactor of the enzyme involved in the conversion of T_4 to T_3. Moreover, The transformation of pre-thyrotropin-releasing hormone involves zinc (TRH) (Baltaci et al. 2013). Thyroglobulin (Tg) and thyroid peroxidase (TPO) are two important thyroid-specific proteins and regulate the information transfer process from tissue-specific DNA to RNA in thyroid hormone. During the information transfer process, transcription binding factors containing zinc bound to cysteine. Besides, the increase of thyroid binding proteins increases serum thyroxine levels, as well as the Zn (Brandao-Net et al. 2016; Alvarez et al. 2015). It was reported that zinc levels of hypothyroid patients were decreased and hyperthyroid patients were increased compared to healthy individuals (Hanif et al. 2018). However, another study found no significant relationship between zinc levels and thyroid hormones in hypothyroidism and hyperthyroidism patients (Razei et al. 2019). Contradictory results were obtained in studies evaluating the effect of zinc on TSH, T_3, and T_4 (Unnikrishnan and Menon 2011; Kolpak et al. 2015). This review aims to assess whether zinc deficiency has an impact on thyroid dysfunction in accordance with current literature.

2. THE PHYSIOLOGICAL AND METABOLIC ROLE OF ZINC

Zinc is the second most abundant transition metal in living organisms, as well as one of the most crucial trace elements for energy metabolism (Chasapis et al.2012). It serves as a cofactor for over 300 metalloenzymes involved in carbohydrate, lipid, and protein metabolism, including carbonic anhydrase, alcohol dehydrogenase, and alkaline phosphatase. Furthermore, zinc is a necessary component of zinc finger proteins, which control DNA transcription. (Franklin et al. 2011). The immune system, antioxidant activity, sensorineural function, structural stability of membranes, transcription, and endocrine function of polynucleotides-particularly thyroid hormone metabolism—are all dependent on zinc for proper operation (Hambidge et al. 2010). A healthy adult has 2-3 g of zinc in his body, and about 60% of it is in muscles, 20-30% in bone, 5% in liver, and 1.6% in the brain. However, dermal and follicular deposited Zinc is about 6% and is not involved in the metabolic processes of the body (Plum et al. 2010).

Only a small portion (about 0.5%) of total zinc is found in the blood circulation. Approximately 80% of blood Zinc is kept in erythrocytes and 16% in the plasma (Chasapis et al. 2012). Besides, 50% of intracellular zinc is in the cytoplasm, 30-40% in the nucleus, and 10% in the plasma membrane (Kambe et al. 2014).

Zinc homeostasis is governed by adaptive mechanisms that regulate mineral absorption as well as excretion. Zinc can be absorbed through simple diffusion, which depends on carrier proteins and concentration (Kambe et al. 2014). Zinc absorption occurs primarily in the proximal small intestine and is regulated by enterocyte carriers. Furthermore, the efficiency of absorption is affected by the luminal concentration of the mineral, as higher absorption rates occur when the amount of zinc in the diet is low (Hunt et al. 2008). The gut cell metallotionin is in charge of the homeostatic regulation of zinc absorption. Several factors, including glucocorticoids and high dietary zinc intake, can affect the gene expression of metallotionin. A cysteine-rich intestinal protein (CRIP) is another protein in the intestinal mucosa that acts as a zinc intracellular carrier and increases absorption rate in cases of deficiency. Zinc is absorbed into the circulation through the basolateral membrane of enterocytes. Thereafter, it binds to proteins and is transported to the liver where it is distributed to various target tissues. Zinc excretion occurs through kidneys, skin, epidermal shedding, and feces (Wang and Zhou, 2010).

The cellular homeostasis of zinc is achieved through complex regulation mechanisms via zinc carriers and metallotionin, which are essential for the absorption, distribution, storage, and flow proteins (Kambe et al. 2013). The SLC39 family, also known as ZIP (Zrt and Irt-like proteins), raises the cytoplasmic zinc concentration by extracting it from the extracellular medium or releasing it from vesicles. Zinc can perform physiological functions in plasma by controlling zinc flow from the cytoplasm to intracellular vesicles or extracellular space via the SLC30 family of ion carriers or ZnTs (Zinc carriers) (Zhao et al. 2013).

The daily zinc intake recommendation is the estimated amount of minerals required to replenish the zinc lost in the body (Hunt et al. 2008). The recommended dietary intake (Recommended Dietary Allowance - RDA) for Zn is 11 mg/day and 8 mg/day for males and females, respectively. The recommended zinc intake during pregnancy and lactation is 11 mg/day and 12 mg/day. The average rate of zinc and fetal tissue accumulation increases progressively in pregnant women, and it is necessary to increase the daily dietary zinc intake, as there is no change observed to balance the intestinal excretion of this mineral (IOM, 2001). Zinc is commonly found in animal foods such as meat, poultry, fish, liver, and seafood which are rich in proteins. Also, beans, soy, and whole grain products are excellent sources of this mineral in the diet (Cesar et al. 2005).

There is no agreement on which indicators are best for determining a population's zinc status. Nevertheless, this evaluation is carried out by measuring various biochemical indicators (Wieringa et al. 2015). Plasma zinc measurement is a widely used biomarker in population screening. This biochemical indicator better reflects the body's zinc status as it is instantly affected by hormonal changes and nutrient intake (Gibson et al. 2008). The measurement of erythrocyte zinc concentration does not reflect the recent level alterations due to the long half-life of erythrocytes. Therefore, it is used as a biochemical indicator to evaluate the previous state of zinc in the body (Santos et al. 2005). However, several factors like infection, inflammation, hemolysis, stress, and homeostasis may change the plasma zinc level which may lead to false determinations. Moreover, the amount of zinc in erythrocytes showed instability in a population study, hence, lead to misinterpretation of the results due to these factors (Pereira et al. 2009).

Recently, there is no universally accepted method to determine the amount of zinc required in an adequate and balanced diet to deeply enlighten the possible relationships between this trace element and chronic diseases. Neverthless, future developments in genome and proteome analysis

technology may improve our understanding of cellular zinc homeostasis and lead to the identification of new markers for the assessment of zinc.

3. ZINC AND THYROID METABOLISM

Although the effect of zinc on thyroid metabolism is not fully explained, it is thought to affect thyroid metabolism through the synthesis and functioning of thyroid hormones (Civitareale et al. 1994; Mahmoodianfard et al. 2015). There are two important proteins specific to the thyroid. These proteins are thyroglobulin (Tg) and thyroperoxidase. Tg is the precursor of T_3 and T_4 and, thyroid peroxidase is the enzyme that catalyzes iodine to Tg. These two proteins regulate the process of information transfer from tissue-specific DNA to RNA in the thyroid hormone (Dumont et al. 1992). There are zinc-related transcription binding factors (TTF1-TTF2) required for gene replacement in the thyroid hormone (Civitareale et al. 1994). TFF 2 is required for Tg and thyroid peroxidase proteins and contains Zn. Zn uptake alters the binding of TTF 2 to RNA. Besides, TPO and Tg activity decrease due to decreased TTF2 activity (Lang et al. 1992).

Zn functions as a regulator of thyroid hormone metabolism and is necessary for TRH synthesis. It binds to T_3 nuclear receptor and mediates gene transcription. Zinc can also affect TSH synthesis in the anterior pituitary. Furthermore, it serves as a crucial transcription factor for the expression of proteins linked to the production of thyroid hormones. (Baltaci et al. 2013; Nishiyama et al. 1994). It has binding sites for Thyroglobulin and thyroperoxidase genes' transcription factors, particularly thyroid transcription factors 1 and 2 (TTF-1 and TTF-2) have crucial roles in gene transcription. TFF 2 is a zinc finger protein that binds to DNA and regulates the redox status of the cell (Civitareale et al. 1994).

T_3 and T_4 are hormones secreted by the thyroid gland that are crucial for preserving cell homeostasis (Severo et al. 2019). The increase of thyroid binding proteins increases serum thyroxine levels, and zinc, as well (Hartoma ve ark., 1979). The T_3 is formed by the deiodination of T_4 (Mahmoodianfard et al. 2015). Deiodinase enzymes (D1-D2-D3) contain three selenoproteins and are involved in the conversion of T_4 to T_3. Zinc functions as the cofactor of the deiodinase enzyme (Marsili et al. 2011; Larsen and Zavacki, 2012). Chen et al. (1998) reported that hepatic type I deiodinase enzyme activities decrease in obese and weak rats fed with a zinc-rich diet. Similarly, in another study, it was stated that the conversion of serum T_4 to T_3 was decreased in rats fed with a zinc-deficient diet (Fujimoto et al. 1986). Conversely, there are also studies that found increased or similar hepatic deiodinase activities

after zinc supplementation (Eybl et al. 2008; Dhawan et al. 2007). Zinc is the cofactor of type II deiodinase, the most active enzyme for the conversion of T_4 to T_3 in humans (Brandão-Neto et al. 2006; Nishiyama et al. 1994; Fujimoto et al. 1986).

Zn is also involved in the TRH conversion of preprothyrotropin-releasing hormone (Mahmoodianfard et al. 2015). TRH secreted from the hypothalamus stimulates the release of TSH in the anterior pituitary and is also involved in T_3 production (Wada King 1986). Morley et al. (1980), found lower T_3 and T_4 levels in zinc-deficient rats compared to those fed with the appropriate amount of zinc (Morley et al. 1980). Ertek et al. stated a positive correlation between serum zinc concentrations and free T_3 in euthyroid participants, and also found a positive correlation between TSH and serum zinc levels in women with normal thyroid function, nodular goiter and autoimmune thyroid (Ertek et al. 2013). In contrast, Brandão-Neto et al. (2006) reported that single-dose oral zinc intake in healthy men did not affect TSH concentrations (Brandão-Neto et al. 2006). A study from Iran included 110 thyroid patients and found a significant decrease in zinc levels of hypothyroid patients compared to healthy individuals. It was determined that there was a relationship between diminished zinc levels and decreased thyroid functions due to the delayed TRH synthesis, decreased T_3, T_4 and TSH levels,, and insufficient conversion of T_4 to T_3 (Rezaei et al. 2019). Similarly, Marques et al. (2010) showed that seven cyclists with low zinc values aged between 24-40 years had a negative relationship between zinc supplement and T_4, but positive between T_3 (Marques et al. 2010). That was explained by the increased activity of type 1 diotironin 5-P deiodinase which is responsible for the conversion of T_4 and T_3. However, zinc supplementation did not cause any significant impact on TSH, T_3, and T_4 values. Moreover, cessation of the zinc supplementation was shown to be positively correlated with the plasma zinc level. In summary, zinc was reported to take place in thyrotropin-releasing hormone synthesis, anterior pituitary, TSH synthesis, T_3 production, and inhibition of deiodinases (Ertek et al. 2010; Raynério Costa and Marreiro, 2006).

The role of zinc finger proteins in mediating site-specific binding to target response elements and receptor dimerization at thyroid hormone receptors has been demonstrated. As a result, thyroid hormone receptor mutations that impair zinc finger function may affect receptor dimerization or DNA binding capacity. (Nagaya et al. 1996). A seven-year-old boy with a zinc finger protein 764 (ZNF764) mutation was found to have higher serum TSH levels and mRNA expression against lower thyroid hormones compared to normal individuals. However, he had thyroid hormone

receptors that were sufficiently expressed. Therefore, According to a report, the interaction of the thyroid hormone receptor coactivators required for the start of the transcriptional activity of zinc finger proteins can account for this resistance to thyroid hormones (Nagaya et al. 1996).

Zinc also protects against cadmium-induced thyroid dysfunction by lowering metal concentrations, maintaining gland weight, and restoring thyroid hormone concentrations to normal levels following an ethanol-rich meal (Baltaci et al. 2004; Pathak et al. 2011). The Zn supplementation in overweight and obese women with hypothyroidism increases serum free T_3 levels (Mahmoodianfard et al. 2015). Since thyroid hormones are closely related to metabolism, T_4 levels decrease when zinc intake is insufficient. However, another study with patients with hypothyroidism and hyperthyroidism, no significant relationship between zinc levels and thyroid hormones was detected (Mahmoodianfard et al. 2015). Blazewicz et al (2010) found that patients with nodular goiter (41.83 ± 7.19 mg / g) had lower serum zinc levels than the control group (101.30 ± 10.90 mg / g) (Błazewicz et al. 2010). It was also reported that serum zinc levels were decreased, and excessive urine excretion was observed in goiter patients (Kandhro et al. 2009). Besides, zinc may also take place in maintaining the volume and shape of the thyroid gland (Ertek et al. 2010; Hammouda et al. 2008). An animal study on mice revealed that zinc deficiency caused to significant structural changes in cells that provide cell apoptosis in follicular cells of the thyroid gland (Ruz et al. 1999). It is well-known that zinc is an important cofactor of superoxide dismutase and glutathione peroxidase activity, it is also crucial to maintain antioxidant balance in the thyroid gland (Ertek et al. 2010; Galazyn-Sidorczuk et al. 2012).

4. CONCLUSION

Zinc is crucial for human health. Its insufficiency is more common particularly excessive grain consuming populations. It has crucial roles in various metabolic reactions, especially in thyroid hormone metabolism. However, the interactions of zinc with thyroid hormones are not exactly explained. Therefore, Future research should clarify the mechanisms by which zinc regulates the metabolism of thyroid hormones and its significance in the management of diseases linked to thyroid gland dysfunction.

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